

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Nimenrix powder and solvent for solution for injection in pre-filled syringe  
Meningococcal group A, C, W-135 and Y conjugate vaccine

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

<i>Neisseria meningitidis</i> group A polysaccharide <sup>1</sup>	5 micrograms
<i>Neisseria meningitidis</i> group C polysaccharide <sup>1</sup>	5 micrograms
<i>Neisseria meningitidis</i> group W-135 polysaccharide <sup>1</sup>	5 micrograms
<i>Neisseria meningitidis</i> group Y polysaccharide <sup>1</sup>	5 micrograms

<sup>1</sup>conjugated to tetanus toxoid carrier protein 44 micrograms

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.  
The powder or cake is white.  
The solvent is clear and colourless.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Nimenrix is indicated for active immunisation of individuals from the age of 6 weeks against invasive meningococcal diseases caused by *Neisseria meningitidis* group A, C, W-135, and Y.

#### 4.2 Posology and method of administration

##### Posology

Nimenrix should be used in accordance with available official recommendations.

##### Primary immunisation

Infants from 6 weeks to less than 6 months of age: two doses, each of 0.5 ml, should be administered with an interval of 2 months between doses.

Infants from 6 months of age, children, adolescents and adults: a single 0.5 mL dose should be administered.

An additional primary dose of Nimenrix may be considered appropriate for some individuals (see section 4.4).

#### Booster doses

After completion of the primary immunisation course in infants 6 weeks to less than 12 months of age, a booster dose should be given at 12 months of age with an interval of at least 2 months after the last Nimenrix vaccination (see section 5.1).

In previously vaccinated individuals 12 months of age and older, Nimenrix may be given as a booster dose if they have received primary vaccination with a conjugated or plain polysaccharide meningococcal vaccine (see sections 4.4 and 5.1).

#### Method of administration

Immunisation should be carried out by intramuscular injection only.

In infants, the recommended injection site is the anterolateral aspect of the thigh. In individuals from 1 year of age, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle (see sections 4.4 and 4.5).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

Nimenrix should under no circumstances be administered intravascularly, intradermally or subcutaneously.

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable effects) and a clinical examination.

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

### Intercurrent illness

Vaccination with Nimenrix should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

### Syncope

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

### Thrombocytopenia and coagulation disorders

Nimenrix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

### Immunodeficiency

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited.

Persons with familial complement deficiencies (for example, C5 or C3 deficiencies) and persons receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *Neisseria meningitidis* groups A, C, W-135 and Y, even if they develop antibodies following vaccination with Nimenrix.

### Protection against meningococcal disease

Nimenrix will only confer protection against *Neisseria meningitidis* group A, C, W-135 and Y. The vaccine will not protect against any other *Neisseria meningitidis* groups.

A protective immune response may not be elicited in all vaccinees.

### *Effect of prior vaccination with plain polysaccharide meningococcal vaccine*

Subjects previously vaccinated with a plain polysaccharide meningococcal vaccine and vaccinated with Nimenrix 30 to 42 months later had lower Geometric Mean Titres (GMTs) measured with a serum bactericidal assay using rabbit complement (rSBA) than

subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years (see section 5.1). The clinical relevance of this observation is unknown.

*Effect of pre-vaccination antibody to tetanus toxoid*

The safety and immunogenicity of Nimenrix was evaluated when it was sequentially administered or co-administered with a vaccine containing, diphtheria and tetanus toxoids, acellular pertussis, inactivated polioviruses (1, 2 and 3), hepatitis B surface antigen and *Haemophilus influenzae* type b polyribosyl ribose phosphate conjugated to tetanus toxoid (DTaP-HBV-IPV/Hib) in the second year of life. The administration of Nimenrix one month after the DTaP-HBV-IPV/Hib vaccine resulted in lower rSBA GMTs against groups A, C and W-135 compared with co-administration (see section 4.5). The clinical relevance of this observation is unknown.

*Immune response in infants aged 6 months to less than 12 months*

A single dose administered at 6 months was associated with lower human complement serum bactericidal assay (hSBA) titres to groups W-135 and Y compared with three doses administered at 2, 4, and 6 months (see section 5.1). The clinical relevance of this finding is unknown. If an infant aged 6 months to less than 12 months of age is expected to be at particular risk of invasive meningococcal disease due to exposure to groups W-135 and Y, consideration may be given to administering a second primary dose of Nimenrix after an interval of 2 months.

*Immune responses in toddlers aged 12-14 months*

Toddlers aged 12-14 months had similar rSBA responses to groups A, C, W-135 and Y at one month after one dose of Nimenrix or at one month after two doses of Nimenrix given two months apart.

A single dose was associated with lower hSBA titres to groups W-135 and Y compared with two doses given two months apart. Similar responses to groups A and C were observed after one or two doses (see section 5.1). The clinical relevance of the findings is unknown. If a toddler is expected to be at particular risk of invasive meningococcal disease due to exposure to groups W-135 and Y, consideration may be given to administering a second dose of Nimenrix after an interval of 2 months. Regarding waning of antibody against group A or group C after a first dose of Nimenrix in children aged 12-23 months, see under Persistence of serum bactericidal antibody titres.

Persistence of serum bactericidal antibody titres

Following administration of Nimenrix there is a waning of serum bactericidal antibody titres against group A when using hSBA (see section 5.1). The clinical relevance of the waning of hSBA antibody titres against group A is unknown. However, if an individual is expected to be at particular risk of exposure to group A and received a dose of Nimenrix more than approximately one year previously, consideration may be given to administering a booster dose.

A decline in antibody titres over time has been observed for groups A, C, W-135 and Y. The clinical relevance of the waning antibody titres is unknown. A booster dose might be considered in individuals vaccinated at toddler age remaining at high risk of exposure to meningococcal disease caused by groups A, C, W-135 or Y (see section 5.1).

#### Effect of Nimenrix on anti-tetanus antibody concentrations

Although an increase of the anti-tetanus toxoid (TT) antibody concentrations was observed following vaccination with Nimenrix, Nimenrix does not substitute for tetanus immunisation.

Giving Nimenrix with or one month before a TT-containing vaccine in the second year of life does not impair the response to TT or significantly affect safety. No data are available beyond the age of 2 years.

### **4.5 Interaction with other medicinal products and other forms of interaction**

In infants, Nimenrix can be given concomitantly with combined DTaP-HBV-IPV/Hib vaccines and with 10-valent pneumococcal conjugate vaccine.

From age 1 year and above, Nimenrix can be given concomitantly with any of the following vaccines: hepatitis A (HAV) and hepatitis B (HBV) vaccines, measles - mumps - rubella (MMR) vaccine, measles - mumps - rubella - varicella (MMRV) vaccine, 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine.

In the second year of life, Nimenrix can also be given concomitantly with combined diphtheria - tetanus - acellular pertussis (DTaP) vaccines, including combination DTaP vaccines with hepatitis B, inactivated poliovirus or *Haemophilus influenzae* type b (HBV, IPV or Hib) such as DTaP-HBV-IPV/Hib vaccine, and 13-valent pneumococcal conjugate vaccine.

In individuals aged 9 to 25 years, Nimenrix can be given concomitantly with human papillomavirus bivalent [Type 16 and 18] vaccine, recombinant (HPV2).

Whenever possible, Nimenrix and a TT containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should be co-administered or Nimenrix should be administered at least one month before the TT containing vaccine.

One month after co-administration with a 10-valent pneumococcal conjugate vaccine, lower Geometric Mean antibody Concentrations (GMCs) and opsonophagocytic assay (OPA) antibody GMTs were observed for one pneumococcal serotype (18C conjugated to tetanus toxoid carrier protein). The clinical relevance of this observation is unknown.

There was no impact of co-administration on immune responses to the other nine pneumococcal serotypes.

One month after co-administration with a combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Tdap) in subjects aged 9 to 25 years, lower GMCs were observed to each pertussis antigen (pertussis toxoid [PT], filamentous haemagglutinin [FHA] and pertactin [PRN]). More than 98% of subjects had anti-PT, FHA or PRN concentrations above the assay cut-off thresholds. The clinical relevance of these observations is unknown. There was no impact of co-administration on immune responses to Nimenrix or the tetanus or diphtheria antigens included in Tdap.

If Nimenrix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

It may be expected that in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There is limited experience with use of Nimenrix in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3).

Nimenrix should be used during pregnancy only when clearly needed, and the possible advantages outweigh the potential risks for the foetus.

##### Breast-feeding

It is unknown whether Nimenrix is excreted in human milk.

Nimenrix should only be used during breast-feeding when the possible advantages outweigh the potential risks.

##### Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects of Nimenrix on the ability to drive and use machines have been performed.

However, some of the effects mentioned under section 4.8 “Undesirable effects” may affect the ability to drive or use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The safety of Nimenrix presented in the table below is based on two clinical study datasets as follows:

- A pooled analysis of data from 9,621 subjects administered a single dose of Nimenrix. This total included 3,079 toddlers (12 months to 23 months), 909 children between 2 and 5 years of age, 990 children between 6 and 10 years of age, 2,317 adolescents (11 to 17 years) and 2,326 adults (18 to 55 years).
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- Data from a study in infants aged 6 to 12 weeks at the time of the first dose (Study MenACWY-TT-083), 1,052 subjects received at least one dose of a primary series of 2 or 3 doses of Nimenrix and 1,008 received a booster dose at approximately 12 months of age.

Safety data have also been evaluated in a separate study, in which a single dose of Nimenrix was administered to 274 individuals aged 56 years and older.

### *Local and general adverse reactions*

In the 6-12 weeks and in the 12-14 months age groups who received 2 doses of Nimenrix given 2 months apart, the first and second doses were associated with similar local and systemic reactogenicity.

The local and general adverse reaction profile of a booster dose of Nimenrix given to subjects from 12 months through 30 years of age after primary vaccination with Nimenrix or other conjugated or plain polysaccharide meningococcal vaccines, was similar to the local and general adverse reaction profile observed after primary vaccination with Nimenrix, except for gastrointestinal symptoms (including diarrhoea, vomiting, and nausea), which were very common among subjects 6 years of age and older.

### Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency categories:

Very common: ( $\geq 1/10$ )

Common: ( $\geq 1/100$  to  $< 1/10$ )

Uncommon: ( $\geq 1/1,000$  to  $< 1/100$ )  
 Rare: ( $\geq 1/10,000$  to  $< 1/1,000$ )  
 Very rare: ( $< 1/10,000$ )

Table 1 shows the adverse reactions reported from the studies in subjects aged from 6 weeks up to 55 years of age and post-marketing experience. Adverse reactions reported in subjects aged  $>55$  years were similar to those observed in younger adults.

<b>Table 1: Tabulated summary of adverse reactions by system organ class</b>		
<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse reactions</b>
Metabolism and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Irritability
	Uncommon	Insomnia Crying
Nervous system disorders	Very common	Drowsiness Headache
	Uncommon	Hypoaesthesia Dizziness
Gastrointestinal disorders	Common	Diarrhoea Vomiting Nausea*
Skin and subcutaneous tissue disorders	Uncommon	Pruritus Rash**
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia Pain in extremity
General disorders and administration site conditions	Very common	Fever Swelling at injection site Pain at injection site Redness at injection site Fatigue
		Common
	Uncommon	Malaise Injection site induration Injection site pruritus Injection site warmth Injection site anaesthesia
	Unknown***	Extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb

\*Nausea and Injection site haematoma occurred at a frequency of Uncommon in infants

\*\*Rash occurred at a frequency of Common in infants

\*\*\*ADR identified post-marketing

### Reporting of suspected adverse reactions



Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

#### **4.9 Overdose**

No case of overdose has been reported.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: vaccines, meningococcal vaccines, ATC code: J07AH08

##### Mechanism of action

Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal activity. Nimenrix induces the production of bactericidal antibodies against capsular polysaccharides of *Neisseria meningitidis* group A, C, W-135 and Y when measured by assays using either rSBA or hSBA.

##### Immunogenicity in infants

Two clinical studies have been conducted in infants, MenACWY-TT-083 and MenACWY-TT-087

In MenACWY-TT-083, the first dose was administered at 6 to 12 weeks of age, the second dose was given after an interval of 2 months and a third (booster) dose was given at the age of approximately 12 months. DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine were co-administered. Nimenrix elicited a bactericidal antibody response against the four meningococcal groups. The response against group C was non-inferior to the one elicited by licensed MenC-CRM and MenC-TT vaccines in terms of percentages with rSBA titres  $\geq 8$  at one month after the second dose. See Table 2.

**Table 2: Bactericidal antibody responses (rSBA\*) and (hSBA\*\*) in infants after two doses given 2 months apart and after a booster dose at 12 months of age (Study MenACWY-TT-083)**

Meningococcal Group	Vaccine group		rSBA*			hSBA**		
			N	≥8 (95% CI)	GMT (95% CI)	N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix	Post dose 2 <sup>(1)</sup>	456	97.4% (95.4; 98.6)	203 (182; 227)	202	96.5% (93.0; 98.6)	157 (131; 188)
		Post booster <sup>(1)</sup>	462	99.6% (98.4; 99.9)	1561 (1412; 1725)	214	99.5% (97.4; 100)	1007 (836; 1214)
C	Nimenrix	Post dose 2 <sup>(1)</sup>	456	98.7% (97.2; 99.5)	612 (540; 693)	218	98.6% (96.0; 99.7)	1308 (1052; 1627)
		Post booster <sup>(1)</sup>	463	99.8% (98.8; 100)	1177 (1059; 1308)	221	99.5% (97.5; 100)	4992 (4086; 6100)
	MenC-CRM vaccine	Post dose 2 <sup>(1)</sup>	455	99.6% (98.4; 99.9)	958 (850; 1079)	202	100% (98.2; 100)	3188 (2646; 3841)
		Post booster <sup>(1)</sup>	446	98.4% (96.8; 99.4)	1051 (920; 1202)	216	100% (98.3; 100)	5438 (4412; 6702)
	MenC-TT vaccine	Post dose 2 <sup>(1)</sup>	457	100% (99.2; 100)	1188 (1080; 1307)	226	100% (98.4; 100)	2626 (2219; 3109)
		Post booster <sup>(1)</sup>	459	100% (99.2; 100)	1960 (1776; 2163)	219	100% (98.3; 100)	5542 (4765; 6446)
W	Nimenrix	Post dose 2 <sup>(1)</sup>	455	99.1% (97.8; 99.8)	1605 (1383; 1862)	217	100% (98.3; 100)	753 (644; 882)
		Post booster <sup>(1)</sup>	462	99.8% (98.8; 100)	2777 (2485; 3104)	218	100% (98.3; 100)	5123 (4504; 5826)
Y	Nimenrix	Post dose 2 <sup>(1)</sup>	456	98.2% (96.6; 99.2)	483 (419; 558)	214	97.7% (94.6; 99.2)	328 (276; 390)
		Post booster <sup>(1)</sup>	462	99.4% (99.1; 99.9)	881 (787; 986)	217	100% (98.3; 100)	2954 (2498; 3493)

The analysis of immunogenicity was conducted on the primary according-to-protocol (ATP) cohort for immunogenicity.

\*rSBA testing performed at Public Health England (PHE) laboratories in UK

\*\*hSBA tested at GSK laboratories

<sup>(1)</sup> blood sampling performed 21 to 48 days post vaccination

Data from MenACWY-TT-083 support the extrapolation of the immunogenicity data and posology to infants from 12 weeks to less than 6 months of age.

In MenACWY-TT-087, infants received either a single primary dose at 6 months followed by a booster dose at 15-18 months (DTPa-IPV/Hib and 10-valent pneumococcal conjugate vaccine was co-administered at both vaccination time points) or three primary doses at 2, 4, and 6 months followed by a booster dose at 15-18 months. A single primary dose administered at 6 months of age elicited robust rSBA responses to groups A, C, W-135 and Y, as measured by the percentage of subjects with rSBA titres  $\geq 8$ , that were comparable to responses after the last dose of a three-dose primary series. A booster dose produced robust responses, comparable between the two dosing groups, against all four meningococcal groups.

Bactericidal antibody responses in infants 6 months of age measured one month after a single primary dose, prior to a booster dose, and one month after a booster dose are presented in Table 3.

<b>Table 3: Bactericidal antibody responses (rSBA* and hSBA**) in infants after one dose at 6 months of age and after a booster dose at 15-18 months of age (Study MenACWY-TT-087)</b>							
Meningo-coccal Group		rSBA*			hSBA**		
		N	$\geq 8$ (95% CI)	GMT (95% CI)	N	$\geq 8$ (95% CI)	GMT (95% CI)
A	Post dose 1 <sup>(1)</sup>	163	98.80% (95.6; 99.9)	1332.9 (1035.2; 1716.2)	59	98.30% (90.9; 100)	271 (206; 355)
	Pre Booster	131	81.70% (74; 87.9)	125.3 (84.4; 186.1)	71	66.20% (54; 77)	21(14; 32)
	Post booster <sup>(1)</sup>	139	99.30% (96.1; 100)	2762.3 (2310.3; 3302.8)	83	100% (95.7; 100)	1416(1140; 1758)
C	Post dose 1 <sup>(1)</sup>	163	99.40% (96.6; 100)	591.6 (482.3; 725.8)	66	100% (94.6; 100)	523 (382; 717)
	Pre Booster	131	65.60% (56.9; 73.7)	27.4 (20.6; 36.6)	78	96.20% (89.2; 99.2)	151 (109; 210)
	Post booster <sup>(1)</sup>	139	99.30% (96.1; 100)	2525.2 (2102.1; 3033.3)	92	100% (96.1; 100)	13360 (10953; 16296)
W	Post dose 1 <sup>(1)</sup>	163	93.90% (89; 97)	1255.9 (917; 1720)	47	87.20% (74.3; 95.2)	137 (78; 238)
	Pre Booster	131	77.90% (69.8; 84.6)	63.3 (45.6; 87.9)	53	100% (93.3; 100)	429 (328; 559)
	Post booster <sup>(1)</sup>	139	100% (97.4; 100)	3144.7 (2636.9; 3750.4)	59	100% (93.9; 100)	9016 (7045; 11537)

Meningococcal		rSBA*			hSBA**		
Y	Post dose 1 <sup>(1)</sup>	163	98.80% (95.6; 99.9)	1469.9 (1186.5; 1821)	52	92.30% (81.5; 97.9)	195 (118; 323)
	Pre Booster	131	88.50% (81.8; 93.4)	106.4 (76.4; 148.1)	61	98.40% (91.2; 100)	389 (292; 518)
	Post booster <sup>(1)</sup>	139	100% (97.4; 100)	2748.6 (2301.4; 3282.6)	69	100% (94.8; 100)	5978 (4747; 7528)

The analysis of immunogenicity was conducted on the primary according-to-protocol (ATP) cohort for immunogenicity.

\*rSBA testing performed at Public Health England (PHE) laboratories in UK

\*\*hSBA tested at Neomed, Laval, Canada

<sup>(1)</sup> blood sampling performed 1 month post vaccination

Serum bactericidal activity was also measured using hSBA as a secondary endpoint. Although similar responses to groups A and C were observed with both dosing schedules, a single primary dose in infants at 6 months was associated with lower hSBA responses to groups W-135 and Y as measured by the percentage of subjects with hSBA titres  $\geq 8$  [87.2% (95% CI: 74.3, 95.2) and 92.3% (95% CI: 81.5, 97.9), respectively] compared with three primary doses at 2, 4, and 6 months of age [100% (95% CI: 96.6, 100) and 100% (95% CI: 97.1, 100), respectively] (see section 4.4). After a booster dose, the hSBA titres to all four serogroups were comparable between the two dosing schedules.

#### Immunogenicity in toddlers aged 12-23 months

In clinical studies MenACWY-TT-039 and MenACWY-TT-040 a single dose of Nimenrix elicited rSBA responses against the four meningococcal groups, with a response against group C that was comparable to the one elicited by the licensed MenC-CRM vaccine in terms of percentages with rSBA titres  $\geq 8$  (Table 4).

**Table 4: Bactericidal antibody responses (rSBA\*) in toddlers aged 12-23 months**

Meningococcal Group	Vaccine group	Study MenACWY-TT-039 <sup>(1)</sup>			Study MenACWY-TT-040 <sup>(2)</sup>		
		N	$\geq 8$ (95%CI)	GMT (95%CI)	N	$\geq 8$ (95%CI)	GMT (95%CI)
A	Nimenrix	354	99.7% (98.4; 100)	2205 (2008; 2422)	183	98.4% (95.3; 99.7)	3170 (2577; 3899)
C	Nimenrix	354	99.7% (98.4; 100)	478 (437; 522)	183	97.3% (93.7; 99.1)	829 (672; 1021)
	MenC-CRM vaccine	121	97.5% (92.9; 99.5)	212 (170; 265)	114	98.2% (93.8; 99.8)	691 (521; 918)
W-135	Nimenrix	354	100% (99.0; 100)	2682 (2453; 2932)	186	98.4% (95.4; 99.7)	4022 (3269; 4949)
Y	Nimenrix	354	100% (99.0; 100)	2729 (2473; 3013)	185	97.3% (93.8; 99.1)	3168 (2522; 3979)

The analysis of immunogenicity was conducted on the ATP cohorts for immunogenicity.

<sup>(1)</sup> blood sampling performed 42 to 56 days post vaccination

<sup>(2)</sup> blood sampling performed 30 to 42 days post vaccination

\* tested at GSK laboratories

In study MenACWY-TT-039, serum bactericidal activity was also measured using hSBA as a secondary endpoint (Table 5).

**Table 5: Bactericidal antibody responses (hSBA\*) in toddlers aged 12-23 months**

Meningococcal Group	Vaccine group	N	Study MenACWY-TT-039 <sup>(1)*</sup>	
			≥8 (95% CI)	GMT (95% CI)
A	Nimenrix	338	77.2% (72.4; 81.6)	19.0 (16.4; 22.1)
C	Nimenrix	341	98.5% (96.6; 99.5)	196 (175; 219)
	MenC-CRM vaccine	116	81.9% (73.7; 88.4)	40.3 (29.5; 55.1)
W-135	Nimenrix	336	87.5% (83.5 ; 90.8)	48.9 (41.2; 58.0)
Y	Nimenrix	329	79.3% (74.5; 83.6)	30.9 (25.8; 37.1)

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.

<sup>(1)</sup> blood sampling performed 42 to 56 days post vaccination

\* tested at GSK laboratories

In Study Men ACWY-TT-104 the immune response following one or two doses of Nimenrix given 2 months apart was evaluated one month after the last vaccination. Nimenrix elicited bactericidal responses against all four groups that were similar in terms of % with rSBA titre ≥8 and GMT after one or two doses (Table 6).

**Table 6: Bactericidal antibody responses (rSBA)\* in toddlers aged 12-14 months**

Meningococcal Group	Vaccine group	Timing	Study MenACWY-TT-104 <sup>(1)</sup>		
			N	≥8 (95% CI)	GMT (95% CI)
A	Nimenrix 1 dose	Post dose 1	180	97.8% (94.4, 99.4)	1437 (1118, 1847)
	Nimenrix 2 doses	Post dose 1	158	96.8% (92.8, 99.0)	1275 (970, 1675)
		Post dose 2	150	98.0% (94.3, 99.6)	1176 (922, 1501)
C	Nimenrix 1 dose	Post dose 1	179	95.0% (90.7, 97.7)	452 (346, 592)
	Nimenrix 2 doses	Post dose 1	157	95.5% (91.0, 98.2)	369 (281, 485)
		Post dose 2	150	98.7%	639

				(95.3, 99.8)	(522, 783)
<b>W-135</b>	<b>Nimenrix 1 dose</b>	Post dose 1	180	95.0% (90.8, 97.7)	2120 (1601, 2808)
	<b>Nimenrix 2 doses</b>	Post dose 1	158	94.9% (90.3, 97.8)	2030 (1511, 2728)
		Post dose 2	150	100% (97.6, 100)	3533 (2914, 4283)
<b>Y</b>	<b>Nimenrix 1 dose</b>	Post dose 1	180	92.8% (88.0, 96.1)	952 (705, 1285)
	<b>Nimenrix 2 doses</b>	Post dose 1	157	93.6% (88.6, 96.9)	933 (692, 1258)
		Post dose 2	150	99.3% (96.3, 100)	1134 (944, 1360)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohort for immunogenicity  
(<sup>(1)</sup>) blood sampling performed 21-48 days post vaccination

\* tested at Public Health England laboratories

In study MenACWY-TT-104, serum bactericidal activity was also measured using hSBA as a secondary endpoint. Nimenrix elicited bactericidal responses against groups W-135 and Y that were higher in terms of % with hSBA titre  $\geq 8$  when two doses were given compared with one. Similar responses in terms of % with hSBA titre  $\geq 8$  were observed with groups A and C (Table 7).

**Table 7: Bactericidal antibody responses (hSBA)\* in toddlers aged 12-14 months**

<b>Meningococcal Group</b>	<b>Vaccine group</b>	<b>Timing</b>	<b>Study MenACWY-TT-104<sup>(1)</sup></b>		
			<b>N</b>	<b><math>\geq 8</math> (95%CI)</b>	<b>GMT (95% CI)</b>
<b>A</b>	<b>Nimenrix 1 dose</b>	Post dose 1	74	95.9% (88.6, 99.2)	118 (87, 160)
	<b>Nimenrix 2 doses</b>	Post dose 1	66	97.0% (89.5, 99.6)	133 (98, 180)
		Post dose 2	66	97.0% (89.5, 99.6)	170 (126, 230)
<b>C</b>	<b>Nimenrix 1 dose</b>	Post dose 1	78	98.7% (93.1, 100)	152 (105, 220)
	<b>Nimenrix 2 doses</b>	Post dose 1	70	95.7% (88.0, 99.1)	161 (110, 236)
		Post dose 2	69	100% (94.8, 100)	1753 (1278, 2404)

<b>W-135</b>	<b>Nimenrix 1 dose</b>	Post dose 1	72	62.5% (50.3, 73.6)	27 (16, 47)
	<b>Nimenrix 2 doses</b>	Post dose 1	61	68.9% (55.7, 80.1)	26 (16, 43)
		Post dose 2	70	97.1% (90.1, 99.7)	757 (550, 1041)
<b>Y</b>	<b>Nimenrix 1 dose</b>	Post dose 1	71	67.6% (55.5, 78.20)	41 (24, 71)
	<b>Nimenrix 2 doses</b>	Post dose 1	56	64.3% (50.4, 76.6)	32 (18, 58)
		Post dose 2	64	95.3% (86.9, 99.0)	513 (339, 775)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohort for immunogenicity

<sup>(1)</sup> blood sampling performed 21-48 days post vaccination

\*tested at GSK laboratories

Persistence of the immune response was evaluated by rSBA and hSBA up to 5 years in children initially vaccinated in study MenACWY-TT-027 (Table 8).

**Table 8: 5 years persistence data in toddlers aged 12-23 months at vaccination (study MenACWY-TT-032; extension of study 027)**

Menin gococc al Group	Vaccine Group	Time- point (year)	rSBA*			hSBA**		
			N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	Nimenrix	4	45	64.4% (48.8; 78.1)	35.1 (19.4; 63.4)	44	52.3% (36.7; 67.5)	8.8 (5.4; 14.2)
		5	49	73.5% (58.9; 85.1)	37.4 (22.1; 63.2)	45	35.6% (21.9; 51.2)	5.2 (3.4; 7.8)
C	Nimenrix	4	45	97.8% (88.2; 99.9)	110 (62.7; 192)	45	97.8% (88.2; 99.9)	370 (214; 640)
		5	49	77.6% (63.4; 88.2)	48.9 (28.5; 84.0)	48	91.7% (80.0; 97.7)	216 (124; 379)
	MenC- CRM vaccine	4	10	80.0% (44.4; 97.5)	137 (22.6; 832)	10	70.0% (34.8; 93.3)	91.9 (9.8; 859)
		5	11	63.6% (30.8; 89.1)	26.5 (6.5; 107)	11	90.9% (58.7; 99.8)	109 (21.2; 557)
W-135	Nimenrix	4	45	60.0% (44.3; 74.3)	50.8 (24.0; 108)	45	84.4% (70.5; 93.5)	76.9 (44.0; 134)
		5	49	34.7% (21.7; 49.6)	18.2 (9.3; 35.3)	46	82.6% (68.6; 92.2)	59.7 (35.1; 101)
Y	Nimenrix	4	45	62.2% (46.5; 76.2)	44.9 (22.6; 89.3)	41	87.8% (73.8; 95.9)	74.6 (44.5; 125)
		5	49	42.9% (28.8; 57.8)	20.6 (10.9; 39.2)	45	80.0% (65.4; 90.4)	70.6 (38.7; 129)

Persistence of immunogenicity was analysed using the year 5 ATP cohort. A selection bias mainly due to revaccination of subjects with group C rSBA titres <8 and their exclusion from subsequent time-point(s) may have led to an overestimation of the titres.

\* rSBA testing performed at PHE laboratories in UK

\*\* tested at GSK laboratories

### Immunogenicity in children aged 2-10 years

In MenACWY-TT-081, Nimenrix was demonstrated to be non-inferior to another licensed MenC-CRM vaccine in terms of vaccine response to group C [94.8% (95% CI: 91.4; 97.1) and 95.7% (95% CI: 89.2; 98.8) respectively], The GMT was lower for the Nimenrix group [2795 (95% CI: 2393; 3263)] versus the MenC-CRM vaccine [5292 (95% CI: 3815; 7340)].

In MenACWY-TT-038, Nimenrix was demonstrated to be non-inferior to the licensed ACWY-PS vaccine in terms of vaccine response to the four groups (A, C, W-135 and Y) (See Table 9).



**Table 9: Bactericidal antibody responses (rSBA\*) to Nimenrix and the ACWY-PS vaccine in children aged 2-10 years 1 month after vaccination (study MenACWY-TT-038)**

Meningococcal Group	Nimenrix			ACWY-PS vaccine		
	N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
A	594	89.1% (86.3; 91.5)	6343 (5998; 6708)	192	64.6% (57.4; 71.3)	2283 (2023; 2577)
C	691	96.1% (94.4; 97.4)	4813 (4342; 5335)	234	89.7% (85.1; 93.3)	1317 (1043; 1663)
W-135	691	97.4% (95.9; 98.4)	11543 (10873; 12255)	236	82.6% (77.2; 87.2)	2158 (1815; 2565)
Y	723	92.7% (90.5; 94.5)	10825 (10233; 11452)	240	68.8% (62.5; 74.6)	2613 (2237; 3052)

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.

VR: vaccine response defined as the proportion of subjects with:

- rSBA titres  $\geq 32$  for initially seronegative subjects (i.e., pre-vaccination rSBA titre  $< 8$ )
- at least a 4-fold increase in rSBA titres from pre- to post-vaccination for initially seropositive subjects (i.e., pre-vaccination rSBA titre  $\geq 8$ )

\* tested at GSK laboratories

Persistence of the immune response was evaluated in children initially vaccinated in MenACWY-TT-081 (Table 10).

**Table 10: 44 months persistence data in children 2-10 years of age at vaccination (Study MenACWY-TT-088; extension of study 081)**

Meningococcal Group	Vaccine Group	Time-point (months)	rSBA*			hSBA**		
			N	$\geq 8$ (95%CI)	GMT (95%CI)	N	$\geq 8$ (95%CI)	GMT (95%CI)
A	Nimenrix	32	193	86.5% (80.9; 91.0)	196 (144; 267)	90	25.6% (16.9; 35.8)	4.6 (3.3; 6.3)
		44	189	85.7% (79.9; 90.4)	307 (224; 423)	89	25.8% (17.1; 36.2)	4.8 (3.4; 6.7)
C	Nimenrix	32	192	64.6% (57.4; 71.3)	34.8 (26.0; 46.4)	90	95.6% (89.0; 98.8)	75.9 (53.4; 108)
		44	189	37.0% (30.1; 44.3)	14.5 (10.9; 19.2)	82	76.8% (66.2; 85.4)	36.4 (23.1; 57.2)
	MenC-CRM vaccine	32	69	76.8% (65.1; 86.1)	86.5 (47.3; 158)	33	90.9% (75.7; 98.1)	82.2 (34.6; 196)
		44	66	45.5% (33.1; 58.2)	31.0 (16.6; 58.0)	31	64.5% (45.4; 80.8)	38.8 (13.3; 113)
W-135	Nimenrix	32	193	77.2% (70.6; 82.9)	214 (149; 307)	86	84.9% (75.5; 91.7)	69.9 (48.2; 101)
		44	189	68.3% (61.1; 74.8)	103 (72.5; 148)	87	80.5% (70.6; 88.2)	64.3 (42.7; 96.8)
Y	Nimenrix	32	193	81.3% (75.1; 86.6)	227 (165; 314)	91	81.3% (71.8; 88.7)	79.2 (52.5; 119)
		44	189	62.4%	78.9	76	82.9%	127

			(55.1; 69.4)	(54.6; 114)		(72.5; 90.6)	(78.0; 206)
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The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.

\* rSBA testing performed at PHE laboratories in UK

\*\* tested at GSK laboratories

Persistence of the immune response was evaluated by hSBA 1 year after vaccination in children 6-10 years of age who were initially vaccinated in study MenACWY-TT-027 (Table 11) (see section 4.4).

**Table 11: 1 month post-vaccination and 1 year persistence data (hSBA\*) in children 6-10 years of age**

Meningococcal Group	Vaccine group	1 month post-vaccination (study MenACWY-TT-027)			1 year persistence (study MenACWY-TT-028)		
		N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	Nimenrix	105	80.0% (71.1; 87.2)	53.4 (37.3; 76.2)	104	16.3% (9.8; 24.9)	3.5 (2.7; 4.4)
	ACWY-PS	35	25.7% (12.5;43.3)	4.1 (2.6;6.5)	35	5.7% (0.7;19.2)	2.5 (1.9;3.3)
C	Nimenrix	101	89.1% (81.3;94.4)	156 (99.3;244)	105	95.2% (89.2;98.4)	129 (95.4;176)
	ACWY-PS	38	39.5% (24.0;56.6)	13.1 (5.4;32.0)	31	32.3% (16.7;51.4)	7.7 (3.5;17.3)
W-135	Nimenrix	103	95.1% (89.0;98.4)	133 (99.9;178)	103	100% (96.5;100)	257 (218;302)
	ACWY-PS	35	34.3% (19.1;52.2)	5.8 (3.3;9.9)	31	12.9% (3.6;29.8)	3.4 (2.0;5.8)
Y	Nimenrix	89	83.1% (73.7;90.2)	95.1 (62.4;145)	106	99.1% (94.9;100)	265 (213;330)
	ACWY-PS	32	43.8% (26.4;62.3)	12.5 (5.6;27.7)	36	33.3% (18.6;51.0)	9.3 (4.3;19.9)

The analysis of immunogenicity was conducted on ATP cohort for persistence.

\* tested at GSK laboratories

### Immunogenicity in adolescents aged 11-17 years and adults aged ≥18 years

In two clinical studies, conducted in adolescents 11-17 years of age (study MenACWY-TT-036) and in adults 18-55 years of age (study MenACWY-TT-035), either one dose of Nimenrix or one dose of the ACWY-PS vaccine were administered.

Nimenrix was demonstrated to be immunologically non-inferior to the ACWY-PS vaccine in terms of vaccine response as defined above (Table 12).

**Table 12: Bactericidal antibody responses (rSBA\*) to Nimenrix and the ACWY-PS vaccine in adolescents aged 11-17 years and adults aged ≥18 years 1 month after vaccination**

Study (Age range)	Menin gococ cal Group	Nimenrix			ACWY-PS vaccine		
		N	VR (95%CI)	GMT (95%CI)	N	VR (95%CI)	GMT (95%CI)
Study MenACWY- TT-036 (11-17 years)	A	553	85.4% (82.1; 88.2)	5928 (5557; 6324)	191	77.5% (70.9; 83.2)	2947 (2612; 3326)
	C	642	97.4% (95.8; 98.5)	13110 (11939; 14395)	211	96.7% (93.3; 98.7)	8222 (6807; 9930)
	W-135	639	96.4% (94.6; 97.7)	8247 (7639; 8903)	216	87.5% (82.3; 91.6)	2633 (2299; 3014)
	Y	657	93.8% (91.6; 95.5)	14086 (13168; 15069)	219	78.5% (72.5; 83.8)	5066 (4463; 5751)
Study MenACWY- TT-035 (18-55 years)	A	743	80.1% (77.0; 82.9)	3625 (3372; 3897)	252	69.8% (63.8; 75.4)	2127 (1909; 2370)
	C	849	91.5% (89.4; 93.3)	8866 (8011; 9812)	288	92.0% (88.3; 94.9)	7371 (6297; 8628)
	W-135	860	90.2% (88.1; 92.1)	5136 (4699; 5614)	283	85.5% (80.9; 89.4)	2461 (2081; 2911)
	Y	862	87.0% (84.6; 89.2)	7711 (7100; 8374)	288	78.8% (73.6; 83.4)	4314 (3782; 4921)

The analysis of immunogenicity was conducted on ATP cohorts for immunogenicity.

VR: vaccine response

\* tested at GSK laboratories

Persistence of the immune response was evaluated up to 5 years after vaccination in adolescents primed in study MenACWY-TT-036 (Table 13).

**Table 13: 5 years persistence data (rSBA\*) in adolescents aged 11-17 years at vaccination**

Menin gococ cal Group	Time- point (Years)	Nimenrix			ACWY-PS vaccine		
		N	≥8 (95%CI)	GMT (95%CI)	N	≥8 (95%CI)	GMT (95%CI)
A	3	449	92.9% (90.1; 95.1)	448 (381; 527)	150	82.7% (75.6; 88.4)	206 (147; 288)
	5	236	97.5% (94.5; 99.1)	644 (531; 781)	86	93.0% (85.4; 97.4)	296 (202; 433)
C	3	449	91.1% (88.1; 93.6)	371 (309; 446)	150	86.0% (79.4; 91.1)	390 (262; 580)
	5	236	88.6% (83.8; 92.3)	249 (194; 318)	85	87.1% (78.0; 93.4)	366 (224; 599)
W-135	3	449	82.0% (78.1; 85.4)	338 (268; 426)	150	30.0% (22.8; 38.0)	16.0 (10.9; 23.6)
	5	236	86.0% (80.9; 90.2)	437 (324; 588)	86	34.9% (24.9; 45.9)	19.7 (11.8; 32.9)
Y	3	449	93.1% (90.3; 95.3)	740 (620; 884)	150	58.0% (49.7; 66.0)	69.6 (44.6; 109)
	5	236	96.6% (93.4; 98.5)	1000 (824; 1214)	86	66.3% (55.3; 76.1)	125 (71.2; 219)

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.

\*rSBA testing performed at PHE laboratories in UK.

Persistence of the immune response was evaluated by hSBA up to 5 years after vaccination in adolescents and adults initially vaccinated in MenACWY-TT-052 (Table 14) (see section 4.4).

**Table 14: 1 month post-vaccination (Study MenACWY-TT-052) and 5 years (Study MenACWY-TT-059) persistence data (hSBA\*) in adolescents and adults 11-25 years of age**

Meningococcal Group	Vaccine Group	Time-point	N	≥8 (95%CI)	GMT (95%CI)
A	Nimenrix	Month 1	356	82.0% (77.6; 85.9)	58.7 (48.6; 70.9)
		Year 1	350	29.1% (24.4; 34.2)	5.4 (4.5; 6.4)
		Year 5	141	48.9% (40.4; 57.5)	8.9 (6.8; 11.8)
C	Nimenrix	Month 1	359	96.1% (93.5; 97.9)	532 (424; 668)
		Year 1	336	94.9% (92.0; 97.0)	172 (142; 207)
		Year 5	140	92.9% (87.3; 96.5)	94.6 (65.9; 136)
W-135	Nimenrix	Month 1	334	91.0% (87.4; 93.9)	117 (96.8; 141)
		Year 1	327	98.5% (96.5; 99.5)	197 (173; 225)
		Year 5	138	87.0% (80.2; 92.1)	103 (76.3; 140)
Y	Nimenrix	Month 1	364	95.1% (92.3; 97.0)	246 (208; 291)
		Year 1	356	97.8% (95.6; 99.0)	272 (237; 311)
		Year 5	142	94.4% (89.2; 97.5)	225 (174; 290)

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.

\* tested at GSK laboratories

In a separate study (MenACWY-TT-085) a single dose of Nimenrix was administered to 194 Lebanese adults 56 years of age and older (including 133 aged 56-65 years and 61 aged >65 years). The percentage of subjects with rSBA titres (measured at GSK's laboratories) ≥128 before vaccination ranged from 45% (group C) to 62% (group Y). Overall, at one month post-vaccination the percentage of vaccines with rSBA titres ≥128 ranged from 93% (group C) to 97% (group Y). In the subgroup aged >65 years the percentage of vaccines with rSBA titres ≥128 at one month post-vaccination ranged from 90% (group A) to 97% (group Y).

Booster response for subjects previously vaccinated with a conjugate meningococcal vaccine against *Neisseria meningitidis*

Nimenrix booster vaccination in subjects previously primed with a monovalent (MenC-CRM) or a quadrivalent conjugate meningococcal vaccine (MenACWY-TT) was studied in subjects from 12 months of age onwards who received a booster vaccination. Robust anamnestic responses to the antigen(s) in the priming vaccine were observed.

Response to Nimenrix in subjects previously vaccinated with a plain polysaccharide vaccine against *Neisseria meningitidis*

In study MenACWY-TT-021 conducted in subjects aged 4.5-34 years, the immunogenicity of Nimenrix administered between 30 and 42 months after vaccination with a ACWY-PS vaccine was compared to the immunogenicity of Nimenrix administered to age-matched subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years. An immune response (rSBA titre  $\geq 8$ ) was observed against all groups (A, C, W-135, Y) in all subjects regardless of the meningococcal vaccine history. The rSBA GMTs were significantly lower in the subjects who had received a dose of ACWY-PS vaccine 30-42 months prior to Nimenrix, however 100% of subjects achieved rSBA titers  $\geq 8$  for all four meningococcal groups (A, C, W-135, Y) (see section 4.4).

Children (2-17 years) with anatomical or functional asplenia

Study MenACWY-TT-084 compared immune responses to two doses of Nimenrix given two months apart between 43 subjects aged 2-17 years with anatomic or functional asplenia subjects and 43 age-matched subjects with normal splenic function. One month after the first vaccine dose and one month after the second dose similar percentages of subjects in the two groups had rSBA titres  $\geq 1:8$  and  $\geq 1:128$  and hSBA titres  $\geq 1:4$  and  $\geq 1:8$ .

**5.2 Pharmacokinetic properties**

Not applicable.

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on local tolerance, acute toxicity, repeated dose toxicity, developmental/reproductive toxicity and fertility studies.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Powder:

Sucrose  
Trometamol

Solvent:

Sodium chloride  
Water for injections

## **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **6.3 Shelf life**

4years

After reconstitution:

After reconstitution, the vaccine should be used promptly. Although delay is not recommended, stability has been demonstrated for 8 hours at 30°C after reconstitution. If not used within 8 hours, do not administer the vaccine.

## **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## **6.5 Nature and contents of container**

Powder in a vial (type I glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe with a stopper (butyl rubber).

Pack sizes of 1 and 10 with or without needles.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

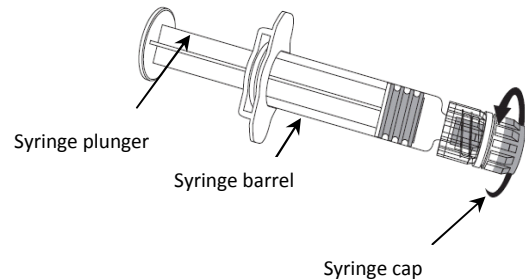
Instructions for reconstitution of the vaccine with the solvent presented in pre-filled syringe

Nimenrix must be reconstituted by adding the entire content of the pre-filled syringe of solvent to the vial containing the powder.

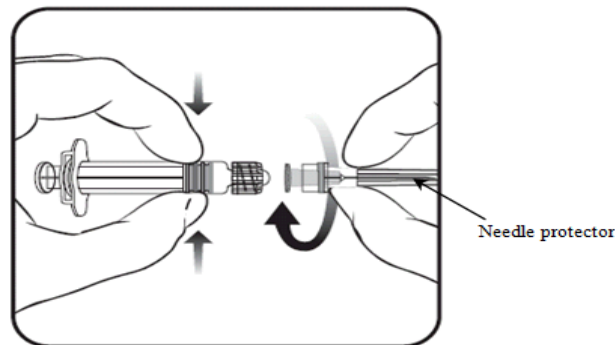
To attach the needle to the syringe, refer to the below picture. However, the syringe provided with Nimenrix might be slightly different (without screw thread) than the

syringe described in the picture. In that case, the needle should be attached without screwing.

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (See picture).
3. Remove the needle protector, which on occasion can be a little stiff.



4. Add the solvent to the powder. After the addition of the solvent to the powder, the mixture should be well shaken until the powder is completely dissolved in the solvent.

The reconstituted vaccine is a clear colourless solution.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be used promptly.

A new needle should be used to administer the vaccine.



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Pfizer Limited  
Ramsgate Road  
Sandwich  
Kent CT13 9NJ  
United Kingdom

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/767/001  
EU/1/12/767/002  
EU/1/12/767/003  
EU/1/12/767/004

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 April 2012  
Date of latest renewal: 16 February 2017

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.